1. INTRODUCTION

The clinical use of stimulants for behavioral disturbances in children and adolescents first began in 1937 at the Emma Pendleton Bradley Home for Children in Rhode Island. Charles Bradley, a psychiatrist, was working with brain-injured children who had received a pneumoencephalogram as part of a standard clinical diagnostic workup. This procedure commonly resulted in severe headache for the children. Bradley decided to use an amphetamine, Benzedrine, in an attempt to ameliorate the headache pain. When given amphetamine, the children demonstrated immediate improvements in their disruptive behaviors. Bradley also noted improved academic performance, better self-control, and improved attention to task. Bradley published his findings in 1950 after using amphetamines for two decades to treat hyperactivity, impulsivity, and moodiness in clinically referred children (1).

In the 1960s the first double-blind placebo-controlled clinical trials of dextroamphetamine and methylphenidate were completed and confirmed Bradley’s initial clinical impressions. Since then, more than 200 controlled trials of stimulants have been completed (2). These studies demonstrate the efficacy of the stimulants in improving the core symptoms of attention deficit hyperactivity disorder (ADHD) and enhancing behavioral, academic, and social functioning in about 50% to 95% of children treated. Variability in response rates is largely because of the presence of comorbid psychiatric and developmental disorders (3–5).

Historically, most of the individuals for whom stimulants were prescribed were school-aged children between 5 and 12 yr of age (6). However, longitudinal studies in ADHD consistently demonstrate the persistence of symptoms and impairment across multiple domains of daily life functioning into adolescence and adulthood in the majority of children diagnosed with ADHD (7,8). Increasingly, stimulants are being prescribed for adolescents and adults meeting criteria for ADHD (9).

Despite the overwhelming amount of research documenting the efficacy of stimulants for the symptoms of ADHD, the stimulants should rarely be the only form of therapy provided to individuals with ADHD. For some cases of mild ADHD, enhanced organizational skills, cognitive behavioral therapies, education about the disorder, and/or school or occupational supports may be sufficient to lessen the impact of the disorder on daily life. However, it is
important to recognize that stimulants are the only treatment modality to date that are known to normalize symptoms of inattention, impulsivity, and overactive behavior in individuals with ADHD (10). Furthermore, the effect size of stimulants has been found to be greater than the effect size of psychosocial therapies for the core symptoms of ADHD, at least over periods of time up to 14 mo (11).

The purpose of this chapter is to review recent advances in stimulant therapy for ADHD, review pharmacodynamic and pharmacokinetic actions of stimulants, and review safety and tolerability data for stimulant use. The emphasis in this chapter is clinical with the overall goal of enhancing the practitioner’s safe and effective clinical use of stimulant medications, particularly in the treatment of ADHD.

2. STIMULANTS

Stimulants are referred to as such because of their ability to activate the level of activity, arousal, or alertness of the central nervous system (CNS). Stimulants in clinical use include racemic methylphenidate, dextromethylphenidate, dextroamphetamine, mixed amphetamine salts (a combination of d-amphetamine and amphetamine), and magnesium pemoline. Pemoline is rarely used because of elevated risk of liver toxicity and is considered a second-line agent for the treatment of ADHD; therefore, it will not be discussed further. Other CNS stimulants, such as caffeine and deanol, are not discussed here because they have not been found to be nearly as effective as the CNS stimulants, and cannot be recommended for clinical use.

2.1. Indications for Use of Stimulant Medications

2.1.1. Established Indications

Established indications for stimulants include ADHD in children, adolescents, and adults. Stimulants are helpful in treating age-inappropriate and impairing symptoms of inattention to task, impulsive behavior, and motor hyperactivity that are not owing to another cause, such as depression, bipolar disorder, anxiety disorders, or psychotic disorders, and are persistently severe enough to cause impaired functioning in school, work, home, or the community. All three subtypes of ADHD (combined, hyperactive-impulsive, and inattentive types) respond to stimulant therapy (3). Narcolepsy is also an established indication for stimulant medications but will not be further discussed here.

2.1.2. Probable Indications

Probable indications for stimulants include the treatment of symptoms of ADHD in preschool children and children with comorbid conditions, such as mental retardation, autism spectrum disorders, head trauma, and seizure disorders (12–21).

Seven out of eight randomized, controlled clinical trials demonstrate the efficacy of stimulants for symptoms of ADHD in 3- to 6-yr old children (12). Compared with older ADHD children, the efficacy of stimulant treatment is more variable, and there is a higher rate of side effects, especially sadness, irritability, clinging behavior, insomnia, and anorexia (22). Stimulant therapy for preschool children should be reserved for particularly severe cases of ADHD, and only after parent management training, family behavioral therapy, and preschool educational supports have been unsuccessful or are unavailable.

Stimulants may be effective for symptoms of ADHD in children with mental retardation. Recent studies support the use of stimulants in the treatment of ADHD symptoms in